

In the Claims¹

Please amend claims 23 and 27-36 as follows:

C 23. (Three times amended) A method for evaluating the ability of a chemical entity to associate with a binding pocket of a molecule or molecular complex, wherein the binding pocket is defined by structure coordinates of all or part of Chinese hamster type II inosine monophosphate dehydrogenase ("IMPDH") amino acids 68, 69, 93, 273, 274, 275, 276, 277, 303, 322, 324, 325, 326, 327, 328, 330, 331, 332, 333, 334, 337, 339, 340, 364, 413, 414, 415, 416, 420, 439, 440, 441, 442, 469, and 470 according to Figure 1, or a homologue of said binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

- a) employing computational means which utilize all or part of said structure coordinates and structure coordinates of a chemical entity, to perform a fitting operation to associate the chemical entity with said binding pocket or homologue thereof;
- b) quantifying the association between the chemical entity and the binding pocket or homologue thereof; and
- c) outputting said quantified association to a suitable output hardware.

C 27. (Amended) The method according to claim 23, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 275, 276, 303, 325, 326, 331, 333 and 441 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

¹ Applicants attach an "Appendix of Amendments" herewith, showing amendments to the claims. Deletions are bracketed and additions are underlined.

28. (Amended) The method according to claim 23, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 274, 275, 276, 277, 303, 322, 324, 325, 326, 331, 333, 414, 415, and 441 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

C²
29. (Twice amended) A method for evaluating the ability of a chemical entity to associate with a binding pocket of a molecule or molecular complex, wherein the binding pocket is defined by structure coordinates of all or part of IMPDH amino acids 67, 68, 69, 70, 73, 274, 275, 276, 303, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 364, 365, 366, 367, 368, 385, 386, 387, 388, 389, 391, 411, 412, 413, 414, 415, 416, 419, 440, 441, 442, 443, 500, 501, 502, 503, 504, 505, and 506 according to Figure 1, or a homologue of said binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

- a) employing computational means which utilize all or part of said structure coordinates and structure coordinates of a chemical entity, to perform a fitting operation to associate the chemical entity with said binding pocket or homologue thereof;
- b) quantifying the association between the chemical entity and the binding pocket or homologue thereof; and
- c) outputting said quantified association to a suitable output hardware.

30. (Amended) The method according to claim 29, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 68, 70, 322, 328, 329, 331, 332, 335, 364, 366, 387, 388, 411, 413, 414, 415, 441, 442, 501, and 502 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

31. (Amended) The method according to claim 29, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 68, 69, 70,

303, 322, 326, 327, 328, 329, 330, 331, 332, 333, 335, 364, 365, 366, 367, 385, 386, 387, 388, 411, 413, 414, 415, 416, 419, 441, 442, 443, 501, 502, 503, and 504 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

32. (Amended) A method for evaluating the ability of a chemical entity to associate with a binding pocket of a molecule or molecular complex, wherein said binding pocket is defined by structure coordinates of all or part of Chinese hamster type II IMPDH amino acids 67, 68, 69, 70, 73, 93, 273, 274, 275, 276, 277, 303, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 337, 339, 340, 364, 365, 366, 367, 368, 385, 386, 387, 388, 389, 391, 411, 412, 413, 414, 415, 416, 419, 420, 439, 440, 441, 442, 443, 469, 470, 500, 501, 502, 503, 504, 505, and 506 according to Figure 1, or a homologue of said binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

- a) employing computational means which utilize all or part of said structure coordinates and structure coordinates of a chemical entity to perform a fitting operation to associate the chemical entity with said binding pocket or homologue thereof;
- b) quantifying the association between the chemical entity and the binding pocket or homologue thereof; and
- c) outputting said quantified association to a suitable output hardware.

33. (Amended) The method according to claim 32, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 68, 70, 275, 276, 303, 322, 325, 326, 328, 329, 331, 332, 333, 335, 364, 366, 387, 388, 411, 413, 414, 415, 441, 442, 501, and 502 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

34. (Amended) The method according to claim 32, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 68, 69, 70, 274, 275, 276, 277, 303, 322, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 335, 364,

365, 366, 367, 385, 386, 387, 388, 411, 413, 414, 415, 416, 441, 442, 443, 501, 502, 503, and 504 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

35. (Amended) The method according to claim 32, wherein said molecule is defined by the set of structure coordinates of IMPDH amino acids according to Figure 1, and said molecular complex is defined by the set of structure coordinates of IMPDH amino acids and one or more of oxidized inosine monophosphate thioimide intermediate (XMP*) and mycophenolic acid (MPA) according to Figure 1, or a homologue thereof, wherein said homologue has a root mean square deviation from the backbone atoms of said IMPDH amino acids of not more than 1.5 Å.

36. (Twice amended) The method according to claim 32, wherein said molecule comprises amino acids 1-514 of IMPDH and said molecular complex comprises amino acids 1-514 of IMPDH, and one or more of oxidized inosine monophosphate thioimide intermediate ("XMP*") and mycophenolic acid ("MPA").

Please add claims 37-62 as follows:

37. (New) The method of claim 32, wherein the fitting operation utilizes energy minimization, shape complementarity or molecular dynamics.

38. (New) A method for identifying an inhibitor to a molecule or molecular complex comprising a binding pocket defined by structure coordinates of all or part of Chinese hamster type II inosine monophosphate dehydrogenase ("IMPDH") amino acids 67, 68, 69, 70, 73, 93, 273, 274, 275, 276, 277, 303, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 337, 339, 340, 364, 365, 366, 367, 368, 385, 386, 387, 388, 389, 391, 411, 412, 413, 414, 415, 416, 419, 420, 439, 440, 441, 442, 443, 469, 470, 500, 501, 502, 503, 504, 505, and 506 according to Figure 1, or a molecule or molecular complex comprising a homologue of the binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

- C³
- a) employing computational means which utilize all or part of said structure coordinates and structure coordinates of a first and a second chemical entity, to perform a fitting operation to associate the first chemical entity and the second chemical entity with said binding pocket or homologue thereof;
 - b) quantifying the association between the first chemical entity and the second chemical entity and the binding pocket or homologue thereof;
 - c) selecting one of said first chemical entity and said second chemical entity based on said quantified association of said first and second chemical entity;
 - d) contacting the selected chemical entity with the molecule or molecular complex;
 - e) monitoring the catalytic activity of the molecule or molecular complex; and
 - f) identifying the chemical entity as an inhibitor based on the effect of the chemical entity on the catalytic activity of the molecule or molecular complex.

39. (New) The method of any one of claims 23, 29 and 32, prior to step a), further comprising the steps of:

- a) producing a crystal of a molecule or molecular complex comprising IMPDH;
- b) determining the three-dimensional structure coordinates of the molecule or molecular complex by X-ray diffraction of the crystal; and
- c) identifying said binding pocket.

40. (New) The method of claim 32, wherein the fitting operation is performed through visual inspection on a computer screen using a computer program capable of generating a three-dimensional graphical representation of said structure coordinates and structure coordinates of said chemical entity.

41. (New) A method of designing a compound or complex that associates with a binding pocket defined by structure coordinates of all or part of Chinese

hamster type II inosine monophosphate dehydrogenase ("IMPDH") amino acids 68, 69, 93, 273, 274, 275, 276, 277, 303, 322, 324, 325, 326, 327, 328, 330, 331, 332, 333, 334, 337, 339, 340, 364, 413, 414, 415, 416, 420, 439, 440, 441, 442, 469, and 470 according to Figure 1, or a homologue of said binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

- C³
- a) employing computational means which utilizes all or part of said structure coordinates and structure coordinates of at least a first chemical entity, to perform a fitting operation to associate said first chemical entity with all or part of the binding pocket or homologue thereof;
 - b) performing a fitting operation to associate at least a second chemical entity with all or part of the binding pocket or homologue thereof;
 - c) quantifying the association between the first and second chemical entity and the binding pocket or homologue thereof;
 - d) repeating steps a) to c) with another first and second chemical entity, selecting a first chemical entity and a second chemical entity based on said quantified association of all of said first and second chemical entity;
 - e) optionally, visually inspecting the relationship of the selected first and second chemical entity to each other in relation to the binding pocket or homologue thereof on a computer screen using the three-dimensional graphical representation of the binding pocket or homologue thereof and said selected first and second chemical entity; and
 - f) assembling the selected first and second chemical entity into a compound or complex that associates with said binding pocket or homologue thereof by model building.

42. (New) The method according to claim 41, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 275, 276, 303, 325, 326, 331, 333 and 441 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

43. (New) The method according to claim 41, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 274, 275, 276, 277, 303, 322, 324, 325, 326, 331, 333, 414, 415, and 441 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

C³

44. (New) A method of designing a compound or complex that associates with a binding pocket defined by structure coordinates of all or part of Chinese hamster type II inosine monophosphate dehydrogenase ("IMPDH") amino acids 67, 68, 69, 70, 73, 274, 275, 276, 303, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 364, 365, 366, 367, 368, 385, 386, 387, 388, 389, 391, 411, 412, 413, 414, 415, 416, 419, 440, 441, 442, 443, 500, 501, 502, 503, 504, 505 and 506 according to Figure 1, or a homologue of said binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

- a) employing computational means which utilizes all or part of said structure coordinates and structure coordinates of at least a first chemical entity, to perform a fitting operation to associate said first chemical entity with all or part of the binding pocket or homologue thereof;
- b) performing a fitting operation to associate at least a second chemical entity with all of part of the binding pocket or homologue thereof;
- c) quantifying the association between the first and second chemical entity and the binding pocket or homologue thereof;
- d) repeating steps a) to c) with another first and second chemical entity, selecting a first and a second chemical entity based on said quantified association of all of said first and second chemical entity;
- e) optionally, visually inspecting the relationship of the selected first and second chemical entity to each other in relation to the binding pocket or homologue thereof on a computer screen using the three-dimensional graphical representation of the binding pocket or homologue thereof and said selected first and second chemical entity; and

f) assembling the selected first and second chemical entity into a compound or complex that associates with said binding pocket or homologue thereof by model building.

45. (New) The method according to claim 44, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 68, 70, 322, 328, 329, 331, 332, 335, 364, 366, 387, 388, 411, 413, 414, 415, 441, 442, 501, and 502 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

C3 46. (New) The method according to claim 44, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 68, 69, 70, 303, 322, 326, 327, 328, 329, 330, 331, 332, 333, 335, 364, 365, 366, 367, 385, 386, 387, 388, 411, 413, 414, 415, 416, 419, 441, 442, 443, 501, 502, 503, and 504 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

47. (New) A method of designing a compound or complex that associates with a binding pocket of a molecule or molecular complex, wherein said binding pocket is defined by the structure coordinates of Chinese hamster type II inosine monophosphate dehydrogenase (IMPDH) amino acids 67, 68, 69, 70, 73, 93, 273, 274, 275, 276, 277, 303, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 337, 339, 340, 364, 365, 366, 367, 368, 385, 386, 387, 388, 389, 391, 411, 412, 413, 414, 415, 416, 419, 420, 439, 440, 441, 442, 443, 469, 470, 500, 501, 502, 503, 504, 505, and 506 according to Figure 1, or a homologue of said binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

a) employing computational means which utilizes all or part of said structure coordinates and structure coordinates of at least a first chemical entity, to perform a fitting operation to associate said first chemical entity with all or part of the binding pocket or homologue thereof;

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- b) performing a fitting operation to associate at least a second chemical entity with all of part of the binding pocket or homologue thereof;
 - c) quantifying the association between the first and second chemical entity and the binding pocket or homologue thereof;
 - d) repeating steps a) to c) with another first and second chemical entity, selecting a first and a second chemical entity based on said quantified association of all of said first and second chemical entity;
 - e) optionally, visually inspecting the relationship of the selected first and second chemical entity to each other in relation to the binding pocket or homologue thereof on a computer screen using the three-dimensional graphical representation of the binding pocket or homologue thereof and said selected first and second chemical entity; and
 - f) assembling the selected first and second chemical entity into a compound or complex that associates with said binding pocket or homologue thereof by model building.

48. (New) The method according to claim 47, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 68, 70, 275, 276, 303, 322, 325, 326, 328, 329, 331, 332, 333, 335, 364, 366, 387, 388, 411, 413, 414, 415, 441, 442, 501, and 502 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

49. (New) The method according to claim 47, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 68, 69, 70, 274, 275, 276, 277, 303, 322, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 335, 364, 365, 366, 367, 385, 386, 387, 388, 411, 413, 414, 415, 416, 441, 442, 443, 501, 502, 503, and 504 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

50. (New) The method according to claim 47, wherein said molecule is defined by the set of structure coordinates of IMPDH amino acids according to Figure

1, and said molecular complex is defined by the set of structure coordinates of IMPDH amino acids and one or more of oxidized inosine monophosphate thioimide intermediate (XMP*) and mycophenolic acid (MPA) according to Figure 1, or a homologue thereof, wherein said homologue has a root mean square deviation from the backbone atoms of said IMPDH amino acids of not more than 1.5 Å.

51. (New) The method according to claim 47, wherein said molecule comprises amino acids 1-514 of IMPDH and said molecular complex comprises amino acids 1-514 of IMPDH, and one or more of oxidized inosine monophosphate thioimide intermediate ("XMP*") and mycophenolic acid ("MPA").

52. (New) A method for screening a plurality of chemical entities for association at a deformation energy of binding of less than -7 kcal/mol with a binding pocket of a molecule or molecular complex, wherein the binding pocket is defined by the structure coordinates of all or part of Chinese hamster type II inosine monophosphate dehydrogenase ("IMPDH") amino acids 68, 69, 93, 273, 274, 275, 276, 277, 303, 322, 324, 325, 326, 327, 328, 330, 331, 332, 333, 334, 337, 339, 340, 364, 413, 414, 415, 416, 420, 439, 440, 441, 442, 469 and 470 according to Figure 1, or a homologue of said binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising steps of:

- a) employing computational means, which utilize all or part of said structure coordinates and structure coordinates of said plurality of chemical entities, to perform a fitting operation between said plurality of chemical entities and the binding pocket or homologue thereof;
- b) quantifying the deformation energy of binding between the plurality of chemical entities and the binding pocket or homologue thereof; and
- c) outputting the chemical entities that associate with the binding pocket or homologue thereof at a deformation energy of binding of less than -7 kcal/mol to a suitable output hardware.

53. (New) The method according to claim 52, wherein said binding pocket is defined by the structure coordinates of IMPDH amino acids 275, 276, 303, 325, 326, 331, 333 and 441 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

54. (New) The method according to claim 52, wherein said binding pocket is defined by the structure coordinates 274, 275, 276, 277, 303, 322, 324, 325, 326, 331, 333, 414, 415 and 441 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

55. (New) A method for screening a plurality of chemical entities for association at a deformation energy of binding of less than -7 kcal/mol with a binding pocket of a molecule or molecular complex, wherein the binding pocket is defined by the structure coordinates of all or part of IMPDH amino acids 67, 68, 69, 70, 73, 274, 275, 276, 303, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 364, 365, 366, 367, 368, 385, 386, 387, 388, 389, 391, 411, 412, 413, 414, 415, 416, 419, 440, 441, 442, 443, 500, 501, 502, 503, 504, 505 and 506 according to Figure 1, or a homologue of said binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

- a) employing computational means, which utilize all or part of said structure coordinates and structure coordinates of said plurality of chemical entities to perform a fitting operation between said plurality of chemical entities and the binding pocket or homologue thereof;
- b) quantifying the deformation energy of binding between the plurality of chemical entities and the binding pocket or homologue thereof; and
- c) outputting the chemical entities that associate with the binding pocket or homologue thereof at a deformation energy of binding of less than -7 kcal/mol to a suitable output hardware.

56. (New) The method according to claim 55, wherein said binding pocket is defined by the structure coordinates of IMPDH amino acids 68, 70, 322, 328, 329, 331, 332, 335, 364, 366, 387, 388, 411, 413, 414, 415, 441, 442, 501 and 502 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

57. (New) The method according to claim 55, wherein said binding pocket is defined by the structure coordinates of IMPDH amino acids 68, 69, 70, 303, 322, 326, 327, 328, 329, 330, 331, 332, 333, 335, 364, 365, 366, 367, 385, 386, 387, 388, 411, 413, 414, 415, 416, 419, 441, 442, 443, 501, 502, 503 and 504 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

58. (New) A method for screening a plurality of chemical entities for association at a deformation energy of binding of less than -7 kcal/mol with a binding pocket of a molecule or molecular complex, wherein the binding pocket is defined by the structure coordinates of all or part of Chinese hamster type II inosine monophosphate dehydrogenase ("IMPDH") amino acids 67, 68, 69, 70, 73, 93, 273, 274, 275, 276, 277, 303, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 337, 339, 340, 364, 365, 366, 367, 368, 385, 386, 387, 388, 389, 391, 411, 412, 413, 414, 415, 416, 419, 420, 439, 440, 441, 442, 443, 469, 470, 500, 501, 502, 503, 504, 505 and 506 according to Figure 1, or a homologue of said binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising steps of:

- a) employing computation means, which utilize all or part of said structure coordinates and structure coordinates of said plurality of chemical entities, to perform a fitting operation between said plurality of chemical entities and the binding pocket or homologue thereof;
- b) quantifying the deformation energy of binding between the plurality of chemical entities and the binding pocket or homologue thereof; and

c) outputting the chemical entities that associate with the binding pocket or homologue thereof at a deformation energy of binding of less than -7 kcal/mol to a suitable output hardware.

59. (New) The method according to claim 58, wherein said binding pocket is defined by the structure coordinates of IMPDH amino 68, 70, 275, 276, 303, 322, 325, 326, 328, 329, 331, 332, 333, 335, 364, 366, 387, 388, 411, 413, 414, 415, 441, 442, 501 and 502 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 \AA .

60. (New) The method according to claim 58, wherein said binding pocket is defined by the structure coordinates of IMPDH amino acids 68, 69, 70, 274, 275, 276, 277, 303, 322, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 335, 364, 365, 366, 367, 385, 386, 387, 388, 411, 413, 414, 415, 416, 441, 442, 443, 501, 502, 503 and 504 according to Figure 1, and the homologue of said binding pocket has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 \AA .

61. (New) The method according to claim 58, wherein said molecule or molecular complex is defined by the set of structure coordinates of IMPDH amino acids according to Figure 1, and said molecular complex is defined by the set of structure coordinates of IMPDH amino acids and one or more of oxidized inosine monophosphate thioimide intermediate (XMP*) and mycophenolic acid (MPA) according to Figure 1, or a homologue thereof, wherein said homologue has a root mean square deviation from the backbone atoms of said IMPDH amino acids of not more than 1.5 \AA .

62. (New) The method according to claim 58, wherein said molecule comprises amino acids 1-514 of IMPDH and said molecular complex comprises amino acids 1-514, and one or more of oxidized inosine monophosphate thioimide intermediate (XMP*) and mycophenolic acid (MPA).